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(54) Title: NOVEL PRODRUGS OF NON-STEROIDAL ANTI-INFLAMMATORY CARBOXYLIC ACIDS, THEIR PREPARATION AND USE

(54) Titre: NOUVEAUX PROMEDICAMENTS A BASE D'ACIDES CARBOXYLIQUES ANTI-INFLAMMATOIRES NON STEROIDIQUES; PREPARATION ET UTILISATION

(57) Abstract

The present invention concerns novel aminoacyloxyalkyl prodrugs of non-steroidal anti-inflammatory carboxylic acids of formula R-COO-R¿1-O-R¿2 wherein R-COO- represents the acyloxy residue of a non-steroidal anti-inflammatory carboxylic acid, R¿1 is a saturated or unsaturated, a straight-chain, branched or cyclic alkylene or alkylidene group of 1 to 8 carbon atoms, which can optionally be substituted, and R¿2 is the aminoacyl residue of a synthetic or natural amino acid, or a secondary, tertiary or quaternary aminoacyl group, as well as the nontoxic pharmaceutically acceptable acid addition salts thereof, methods for preparing the said prodrug forms, pharmaceutical compositions containing such prodrug forms, and methods for using the prodrug forms.

(57) Abrégé

La présente invention concerne de nouveaux promédicaments d'aminoacyloxyalkyl à base d'acides carboxyliques anti-inflammatoires non stéroïdiques représentés par la formule R-COO-R¿1-O-R¿2. Dans cette formule, R-COO- représente le résidu acyloxy d'un acide carboxylique anti-inflammatoire non stréroïdique, R¿1 est un groupe alkyle inférieur, qui peut être un groupe alkylène ou alkydiène à chaîne droite, ramifiée ou cyclique, saturé ou insaturé, de 1 à 8 atomes de carbone, éventuellement substitué, et R¿2 est un résidu aminoacyle d'un amino-acide synthétique ou naturel, ou bien un groupe aminoacyle secondaire, tertiaire ou quaternaire, ainsi que des sels d'addition acide non toxiques, acceptables au plan pharmaceutique, de ces composés. De plus, l'invention concerne également des procédés de préparation de ces promédicaments, des compositions pharmaceutiques renfermant ces promédicaments et des méthodes d'administration desdits promédicaments.

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The present invention concerns novel aminoacyloxyalkyl prodrugs of non-steroidal anti-inflammatory carboxylic acids of formula R-COO-R_1-O-R_2 wherein R-COO- represents the acyloxy residue of a non-steroidal anti-inflammatory carboxylic acid, R_1 is a saturated or unsaturated, a straight-chain, branched or cyclic alkylene or alkylidene group of 1 to 8 carbon atoms, which can optionally be substituted, and R_2 is the aminoacyl residue of a synthetic or natural amino acid, or a secondary, tertiary or quaternary aminoacyl group, as well as the nontoxic pharmaceutically acceptable acid addition salts thereof, methods for preparing the said prodrug forms, pharmaceutical compositions containing such prodrug forms, and methods for using the prodrug forms.

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Novel prodrugs of non-steroidal anti-inflammatory carboxylic acids, their preparation and use

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel highly bioreversible prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs) containing one or more carboxylic acid groups, and specifically to aminoacyloxyalkyl derivatives, to methods for preparing the said prodrug forms, to pharmaceutical compositions containing such prodrug forms, and to methods for using the prodrug forms. In particular, the present invention relates to novel aminoacyloxyalkyl prodrugs of NSAIDs characterized as being more permeable through biological membranes, especially through the skin after topical administration, and less irritating to membranes.

BACKGROUND OF THE INVENTION

It is well-known that the non-ionized form of a drug molecule is absorbed more efficiently than its ionized form. Non-steroidal anti-inflammatory carboxylic acids are significantly ionized and thus hydrophilic in their chemical character at physiological pH. In case of a charged drug molecule, the positively charged drug molecule is more permeable across the negatively charged skin-membrane than the negatively charged drug molecule. Thus the non-steroidal anti-inflammatory carboxylic acids have poor permeation across biological lipid-water membranes, especially across the skin. This limits their pharmaceutical use, especially their topical administration.

Acidic NSAIDs are irritating to the mucous membrane of the gastro-intestinal (GI) tract. Topical (i.e. dermal) application of NSAIDs would eliminate the irritation to the GI tract and harmful systemic side-effects due to high systemic drug concentrations after oral administration. In addition, topical application would be more suitable for treatment of local inflammatory and pain conditions due to higher local drug concentration. Unfortunately, the non-steroidal anti-inflammatory carboxylic acids do not readily pass through skin due to the reasons mentioned above.

A promising approach to eliminate the drawbacks due to the carboxylic acid group of the drug molecule is to prepare ester-prodrugs. Prodrugs are pharmacologically inactive derivatives of drug molecules that require a chemical or favorably enzymatic transformation in order to release the active drug within the body. Thus, the object of the present invention is to design and prepare novel bioreversible prodrugs of NSAIDs containing at least one carboxylic acid group, which are chemically stable in a non-enzyme medium, have suitable aqueous and lipid solubility (able to permeate through the biological membranes, especially through the skin), are not significantly ionized or are positively charged at physiological pH and readily hydrolyze to the parent drug after or during skin permeation *in vivo*. The present novel aminoacyloxyalkyl double-esters of NSAIDs fulfill the above-mentioned desirable attributes.

Numerous derivatives of non-steroidal anti-inflammatory carboxylic acids have been reported but only a limited number of the reported derivatives are bioreversible prodrugs of NSAIDs. Sloan (US 4,206,220) disclosed various amide-prodrugs of NSAIDs, Ladkani et al. (EP 0 112 130 B1) disclosed ethoxycarbonyloxy ethyl ester prodrugs of NSAIDs, Bundgaard (EP 0 278 977 B1) disclosed NSAIDs esters of various hydroxy-amides and Sloan and Roy (EP 0 039 051 A2) disclosed Mannich-base hydroxamic acid prodrugs of NSAIDs. In addition, various prodrugs of NSAIDs, but not aminoacyloxyalkyl double-esters, are described in the following publications: Pharm Res 6: 867-873, 1989; Pharm Res 10: 1191-1199, 1993; J Pharm Sci 81: 149-154, 1992; Biopharm Drug Disposit 16: 201-210, 1995; Pharmazie 51: 30-33, 1996; In t J Pharm 124: 45-51, 1995; Int J Pharm 77:21-29, 1991; J Control Rel 34: 223-232, 1995; J Pharm Sci 83: 1578-1581, 1994; Pharm Res 9: 492-496, 1992; Pharmazie 49:422-424, 1994.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns novel bioreversible aminoacyloxyalkyl prodrugs of non-steroidal anti-inflammatory carboxylic acids of the formula

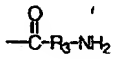
$$R\text{-}COO\text{-}R_1\text{-}O\text{-}R_2 \qquad (I)$$

wherein:

R-COO- represents the acyloxy residue of a carboxylic acid group containing non-steroidal anti-inflammatory agent, i.e. of a non-steroidal anti-inflammatory carboxylic acid R-COOH,

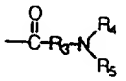
R_1 represents a saturated or unsaturated, straight-chain, branched or cyclic alkylene or alkylidene group of 1 to 8 carbon atoms, which can optionally be substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono- or dialkylamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy,

R_2 is an aminoacyl residue of a synthetic or natural amino acid of the formula



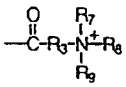
wherein R_3 represents a saturated or unsaturated, straight-chain or branched alkylene or alkylidene group of 1 to 8 carbon atoms, which may be substituted with 1 to 3 groups selected from amino, mono- or dialkylamino, acylamino, hydroxyl, thiol, methylthiol, carboxyl, and phenyl,

or R_2 is a secondary or tertiary aminoacyl group of the formula



wherein R_3 is as hereinabove defined; R_4 and R_5 are the same or different and are selected from hydrogen, a straight-chain or branched C_1-C_6-alkyl group, which is optionally substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono- or dialkyamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy, or R_4 and R_5, together with the nitrogen, form a cyclic heteroalkyl radical or a heteroaryl radical,

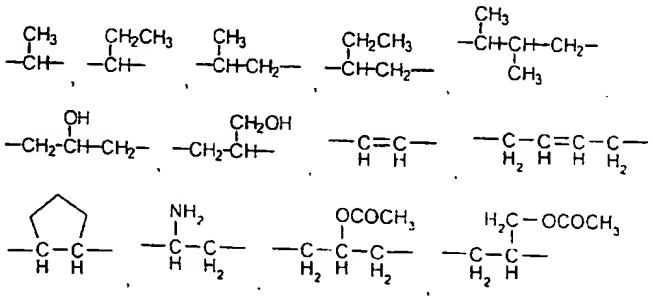
or R_2 is a quaternary aminoacyl group of the formula



wherein R_3 is as hereinabove defined and R_7, R_8 and R_9 are the same or different and are selected from hydrogen, a straight-chain or branched C_1-C_6-alkyl group, which optionally is substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono- or dialkyamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyan, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy, as well as the nontoxic pharmaceutically acceptable acid addition salts thereof.

According to the invention, the non-steroidal anti-inflammatory agent comprising at least one carboxylic acid group is preferably selected from the group consisting of: naproxen; ketoprofen; ibuprofen; fenoprofen; flurbiprofen; oxaprofen; diclofenac; tolmetin; tolfenamic acid; mefenamic acid; sulindac; indomethacin; salicylic acid; acetylsalicylic acid; diflunisal; loxoprofen; indoprofen; pirprofen; clidanac; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceclofenac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; bromfenac; fenclofenac; alcofenac; orpanoxin; zomopirac; flufenamic acid; niflumic acid; pranoprofen; zaltoprofen; suprofen; and ketorolac.

Specific examples of R_1 as a lower alkylene group include methylene, ethylene, trimethylene, tetramethylene,



R_2 is advantageously the aminoacyl residue of alanine, glycine, glycylglycine, arginine, cysteine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, hydroxyproline, serine, valine, tryptophan, tyrosine, threonine, ornithine, α-aminobutyric acid, norvaline, or norleucine.

Unless otherwise specified, the various groups and radicals mentioned above and below

have the following meaning.

Alkyl or alkenyl as such or as part of another goup, such as in mono- and dialkylamino, alkylcarbonyl, aralkyl, acyl, alkoxy, alkenyloxy, and alkylcarbonyloxy, means a group containing 1-6 carbon atoms, preferably 1-4 carbon atoms.

Halogen means iodine, fluorine, bromine or chlorine.

Aryl as such or in aroyl and aralkyl means an aromatic group containing up to 10 carbon atoms, and is preferably phenyl or naphtyl, which can be substituted with 1 to 3 substituents selected from lower alkyl with 1 to 4 carbon atoms, hydroxy, halogen, nitro or amino.

Acyl as such or in acylamino is an aliphatic acyl group containing an alkyl or alkenyl group as defined.

The cycloheteroalkyl radical formed from R_4 and R_5 is preferably morpholinyl, thiomorpholinyl, 1-pyrrolidinyl, piperidinyl, piperazinyl or 4-alkyl-1-piperazinyl, such as 4-lower alkyl-1-piperazinyl, e.g. 4-methyl-1-piperazinyl. A heteroaryl radical is preferably imidazolyl, indoxyl, indolizinyl, oxazolyl, thiazolyl or 1-pyrazolyl.

The novel compounds of the invention can be prepared in the following manner. In a first step, the carboxyl function of a non-steroidal anti-inflammatory agent R-COOH or its acid salt $R\text{-}COO^-M^+$ is esterified, under S_N2 conditions, with a compound $X\text{-}R_1\text{-}OH$ to yield the intermediate II, e.g. according to the following reaction scheme:

$$R\text{-}COO^-M^+ + X\text{-}R_1\text{-}OH \text{ -----> } R\text{-}COO\text{-}R_1\text{-}OH + X^-M^+$$

II

wherein X is a suitable leaving group, e.g., chlorine, tosylate, iodine etc., preferably bromine and R_1 is as above defined. Suitable acid salts are the alkaline metal and amine salts, for example, lithium, sodium, potassium, tetrabutylammonium and triethylammonium salts. In the present invention the sodium salt is preferred. The

reaction is ordinarily carried out in a dipolar aprotic solvent which does not take part in the reaction, preferably in dimethylformamide or hexamethylphosphoric triamide.

A second method for preparing the intermediate II comprises reacting an acid R-COOH or a reactive derivative of the acid, such as a halide, an anhydride or a mixed anhydride of the formula R-COZ, wherein Z means the activating group, such as a halide or anhydride residue, with a compound HO-R_1-OH, wherein R_1 is as above defined, according to the following reaction scheme:

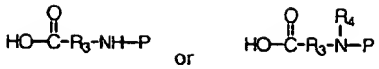
R-COZ + HO-R_1-OH ----> R-COO-R_1-OH + HZ

II

The most useful reactive derivative is the acid chloride (Z=Cl), which can be prepared from the corresponding acid by reaction with thionyl chloride or oxalyl chloride. The reaction is ordinarily carried out in the presence of an acid eliminator, such as a tertiary amine, for example pyridine, trimethylamine, triethylamine etc, an alkali carbonate, an alkali hydroxide, a metal hydride or the like, usually in a suitable solvent which does not take part in the reaction and which includes, for example, ether, tetrahydrofuran, benzene, toluene, chloroform, dichloromethane and the like.

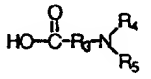
When using a free acid as the starting material the reaction must be carried out in the presence of a condensing agent, such as a carbodiimide, e.g. N,N-dicyclohexylcarbodiimide. The reaction utilizing an acid starting material is conveniently carried out in an inert solvent, such as dichloromethane, ethyl acetate, tetrahydrofuran or the like. A catalyst, such as p-toluenesulphonic acid or 4-(N,N-dimethylamino)pyridine, may be added. Alternatively, the condensing agent can be a 2-halo-1-alkylpyridinium salt, or a combination of diethylazodicarboxylate and triphenylphosphine.

In a second step the intermediate II is reacted in the presence of condensing agent with a protected primary or secondary amino acid of the formula



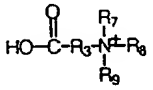
wherein R_3 and R_4 are as hereinabove defined and P is a protecting group, for example t-butyloxycarbonyl (Boc),

or with a tertiary amino acid of the formula,



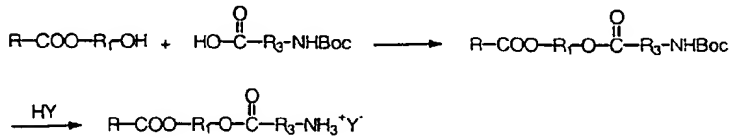
wherein R_3, R_4 and R_5 are as hereinabove defined,

or with a quaternary amino acid of the formula:



wherein R_3, R_7, R_8 and R_9 are as hereinabove defined.

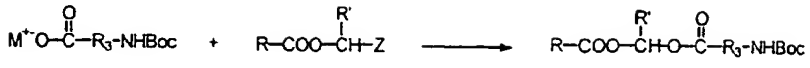
The primary and secondary amine functions of the amino acids must be protected e.g. with a t-butyloxycarbonyl (Boc) protective group. The Boc-protective group is removed by protonation with an anhydrous acid, HY, such as p-toluenesulphonic acid, HCl, or trifluoroacetic acid in ethyl acetate, in dichloromethane, tetrahydrofuran or any other common reagent for removing the Boc-protective group in amino acid chemistry, to give the salt III of the compound according to the following scheme:



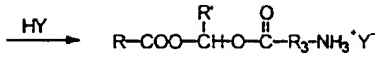
III

In case R_1 is a substituted or unsubstituted methylene group (-CHR'- or $-CH_2-$), these compounds can be prepared by condensing an acid salt of a Boc-protected amino acid V with a halide ester VI of a non-steroidal anti-inflammatory agent and removing the Boc- protective group by protonation with an anhydrous acid, HY, according to

following scheme:



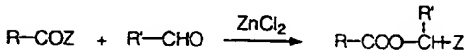
V VI



IV

In the above formulae, R' has the meaning of hydrogen, a straight or branched alkyl group, preferably an optionally substituted lower alkyl group with 1 - 6 C-atoms as defined for R_4 and R_5, or an optionally substituted aryl or aralkyl group, as defined above, and Z the meaning of a halide, preferably the chloride, but can also be the bromide or iodide. Suitable acid salts (compound V) are the alkaline metal and amine salts, for example, lithium, sodium, potassium, tetrabutylammonium and triethylammonium salts.

The halide ester VI can be prepared by the reaction of an acid halide R-COZ where Z is preferably the chloride, but can also be the bromide or iodide, with an aliphatic aldehyde VII by heating the reagents together in the presence of anhydrous zinc chloride according to the following scheme:



VII VI

The novel prodrugs according to the invention may be used to treat any condition for which the parent carboxy containing NSAID is useful. The prodrug according to the invention can be administered for example orally, parenterally, topically or rectally by means of any pharmaceutical formulation useful for said administration, and containing the said prodrug in pharmaceutically acceptable amounts together with pharmaceutically acceptable carriers, adjuvants or vehicles known in the art. The manufacture of such pharmaceutical formulations is well known in the art.

Thus the pharmaceutical composition may be in a dosage form suitable for oral use, such as tablets, capsules, liquid dosage forms, such as suspensions, emulsions, syrups etc. All such formulations are made using per se known formulation techniques and carriers, adjuvants and additives. The prodrugs according to the invention may also be administered parenterally, for example using aqueous or oily suspensions, emulsions, or dispersions containing the active agent in combination with conventional pharmaceutically acceptable excipients. Formulations for rectal use are e.g. suppositories containing the active prodrug in combination with carrier subtstances suitable for rectal use.

Especially contemplated within the invention is the topical administration of the prodrug, for which administration form creams, ointments, jellies, solutions, suspensions or the like are useful which contain a pharmacologically active amount of the said prodrug together with a per se known pharmaceutically acceptable carrier or vehicle.

The therapeutic dose to be given to a patient in need of treatment will vary depending i.a. on the body weight and age of the patient, the particular condition being treated. as well as the manner of administration and are easily determined by a person skilled in the art. Typically a dosage or concentration similar to or less than that of the parent drug would be acceptable. Generally a concentration of 0.01% to 5% of active agent in a suitable carrier would be sufficient for topical use, whereas a dosage form for oral use of 0.1 mg to 5 g, typically 0.1 mg to 500 mg would be suitable for most purposes.

The following examples illustrate the invention without limiting the same in any way.

Example 1

2-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -CH_2CH_2- ; R_2 = -$COCH_2$-NH_2)

a) 2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate

A mixture of 2-(6-methoxy-2-naphthyl)propanoate sodium salt (900 mg, 3.6 mmol) and 2-bromoethanol (445 mg, 3.6 mmol) in dry N,N-dimethylformamide (20 mL) was stirred at 60 °C for 24 h. Water (50 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with a 5% aqueous solution of $NaHCO_3$ (2 x 25 mL) and water (2 x 25 mL), dried over anhydrous $CaSO_4$, filtered and evaporated in vacuo to give the desired compound (0.8 g, 82%).

b) 2-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

A mixture of 2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate, (1.1 g, 4.2 mmol), Boc-glycine (730 mg, 4.2 mmol), 4-(N,N-dimethylamino)pyridine (25 mg, 0.2 mmol) and N,N'-dicyclohexylcarbodiimide (1.13 g, 5.5 mmol) in dry dichloromethane (60 mL) was stirred at 60 °C for 24 h. The precipitated dicyclohexylurea was filtered off and the filter cake was washed with dichloromethane. The filtrate was evaporated, and the residue was treated with trifluoroacetic acid:dichloromethane (1:1, 14 mL) at 25 °C for 3 h followed by concentration under vacuum. The free base was generated by dissolving the residue in a 5% aqueous solution of $NaHCO_3$ (2 x 25 mL) and extracting the free amine using ethyl acetate (2 x 50 mL). The organic layer was dried over anhydrous $CaSO_4$, filtered and evaporated in vacuo. The residue obtained was dissolved in diethyl ether and treated with saturated diethyl ether-HCl to give 2-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate hydrochloride salt (1.20 g, 78 %): mp 113-4 °C; ^1H NMR ($CDCl_3/CD_3OD$ 8:2, 400 MHz): δ 7.65, 7.37, 7.71, 7.12, 7.13, 7.69, 3.90, 3.87, 1.57, 4.30, 3.66.

Example 2

2-(L-leucyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -CH_2CH_2- ; R_2 = -$COCH[CH_2CH(CH_3)_2]$-NH_2)

The compound was prepared as described in the example 1 from 2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate (1.1 g, 4.2 mmol) and Boc-L-leucine (0.9 g, 4.2 mmol).

Obtained as HCl salt (0.99 g, 56%); mp. 96-7 °C. ^{1}H NMR ($CDCl_3/CD_3OD$ 8:2, 400 MHz): δ 7.64, 7.38, 7.72, 7.16, 7.12, 7.69, 3.88, 3.90, 1.57, 4.39/4.33*, 4.41, 3.88, 1.65, 1.71, 0.89, 0.88 (*due to the chiral center, the CH_2 protons are not equivalent); HR-MS: Calculated mass for $C_{22}H_{29}NO_5$: 387.205. Measured mass: 387.207.

Example 3

2-(L-isoleucyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -CH_2CH_2- ; R_2 = -COCH[CH(CH_3)CH_2CH_3]-NH_2)

The compound was prepared as described in the example 1 from 2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate (0.7 g, 2.5 mmol) and Boc-L-isoleucine (0.6 g, 2.5 mmol). Obtained as HCl salt (0.95 g, 90%); mp 99-100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65, 7.38, 7.72, 7.14, 7.15, 7.70, 3.91, 3.88, 1.58, 4.49/4.30*, 4.33, 3.84, 1.90, 0.88, 1.37/1.20*, 0.84, 8.52 (*due the to chiral center, the CH_2 protons are not equivalent); HR-MS: Calculated mass for $C_{22}H_{29}NO_5$: 387.205. Measured mass: 387.201.

Example 4

2-(L-phenylalanyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -CH_2CH_2- ; R_2 = -COCH[$CH_2C_6H_5$]-NH_2)

The compound was prepared as described in the example 1 from 2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate (0.8 g, 2.9 mmol) and Boc-L-phenylalanine (0.8 g, 2.9 mmol). Obtained as HCl salt (370 mg, 28%); mp. 187-8 °C. ^{1}H NMR ($CDCl_3/CD_3OD$ 8:2, 400 MHz): δ 7.63, 7.37, 7.67, 7.05, 7.10, 7.64, 3.88, 3.88, 1.58, 4.39/4.29*, 4.26, 4.09, 3.03, 7.11, 7.28 (*due to the chiral center, the CH_2 protons are not equivalent); HR-MS: Calculated mass for $C_{25}H_{27}NO_5$: 421.189. Measured mass: 421.200.

Example 5

3-(glycyloxy)propyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -$CH_2CH_2CH_2$- ; R_2 = -COCH$_2$-NH_2)

a) 3-hydroxypropyl 2-(6-methoxy-2-naphthyl) propanoate

The compound was prepared as described in the example 1 from the sodium salt of 2-(6-methoxy-2-naphthyl)propanoate (900 mg, 3.6 mmol) and 3-bromo-1-propanol (500 mg, 3.6 mmol) to give the desired compound (0.50 g, 48%).

b) 3-(glycyloxy)propyl 2-(6-methoxy-2-naphthyl)propanoate

Obtained as free amine (0.60 g, 72 %) from 3-hydroxypropyl 2-(6-methoxy-2-naphthyl) propanoate (0.70 g, 2.4 mmol) and Boc-glycine (0.40 g, 2.4 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60, 7.32, 7.65, 7.07, 7.10, 7.65, 3.85, 3.81, 1.52, 4.07, 1.86, 4.11, 3.73, 8.15. HR-MS: Calculated mass for $C_{19}H_{23}NO_5$: 345.158. Measured mass: 345.165.

Example 6

4-(L-isoleucyloxy)butyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -$CH_2CH_2CH_2CH_2$- ; R_2 = -COCH[$CH(CH_3)CH_2CH_3$]-NH_2)

a) 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate

The compound was prepared as described in the example 1 from the sodium salt of 2-(6-methoxy-2-naphthyl)propanoate (900 mg, 3.6 mmol) and 4-bromo-1-butanol (500 mg, 3.6 mmol) to give the desired compound (0.12 g, 22%).

b) 4-(L-isoleucyloxy)butyl 2-(6-methoxy-2-naphthyl)propanoate

4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (0.83 g, 2.7 mmol) and Boc-L-isoleucine (0.63 g, 2.7 mmol) 4-(N,N-dimethylamino)pyridine (0.49 mg, 4.0 mmol) and N,N'-dicyclohexylcarbodiimide (0.83 g, 4.0 mmol) in dry dichloromethane (60 mL) was stirred at room temperature for 36 h. The precipitated dicyclohexylurea was filtered off and the filter cake was washed with dichloromethane. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography eluting with 20% ethyl acetate in petroleum ether to give Boc-protected 4-(L-isoleucyloxy)butyl ester of naproxen (0.96 g, 69 %) as an oil. The Boc-protected ester (420 mg, 0.81 mmol) was treated with 2 N HCl/ ethyl acetate (8 mL) and stirred at room temperature for 3h followed by concentration under vacuum. The residue was recrystallized from ethyl acetate to give 4-(L-isoleucyloxy)butyl 2-(6-methoxy-2-naphthyl)propanoate hydrochloride salt (340 mg, 92 %): mp 72-3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64, 7.38, 7.69, 7.10, 7.13, 7.69, 3.84, 3.90, 1.56, 4.07, 1.62, 4.12, 3.96, 2.15, 1.06, 1.41/1.46*, 0,91, 8.82 (*due to the chiral center, the CH_2 protons are not equivalent); HR-MS: Calculated mass for $C_{24}H_{33}NO_5$: 415.236. Measured mass: 415.222.

Example 7

4-(L-phenylalanyloxy)butyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH_2CH_2CH_2CH_2-$; R_2 = $-COCH[CH_2C_6H_5]-NH_2$)

Obtained as the free amine from 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (0.5 g, 1.7 mmol) and Boc-L-phenylalanine (0.45 g, 1.7 mmol) according to the method described in the example 1. The free amine was purified by flash silica gel column chromatography (30 mL/20 mm column) eluting with 20 % methanol in ethyl acetate to afford 4-(L-phenylalanyloxy)butyl 2-(6-methoxy-2-naphthyl)propanoate (220 mg, 41%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66, 7.40, 7.70, 7.10, 7.13, 7.70, 3.90, 3.84, 1.58, 4.01, 1.54, 4.06, 3.68, 3.01/2.83*, 7.16, 7.27, 7.22; (*due to the chiral center, the CH_2 protons are not equivalent); HR-MS: Calculated mass for $C_{27}H_{31}NO_5$: 449.220. Measured mass: 449.225.

Example 8

1-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH(CH_3)-$; R_2 = $-COCH_2-NH_2$)

a) 1-chloroethyl 2-(6-methoxy-2-naphthyl)propanoate

To a cooled (0-5 °C) mixture of acetaldehyde (3 mL), anhydrous $ZnCl_2$ (200 mg) in dry dioxane (10 mL) naproxen acid chloride (2.56 g, 10.3 mmol) was added dropwise over period of 1h. After complete addition, the bath was removed, the contents was allowed to warm to room temperature and the reaction mixture was stirred for 16 hours. The mixture was extracted with diethyl ether and washed with a 5% $NaHCO_3$-solution and water. Purification with flash silica gel column eluting with 20% ethyl acetate in petroleum ether afforded 1-chloroethyl 2-(6-methoxy-2-naphthyl)propanoate as a yellow oil (1.49 g, 51%). ^1H NMR ($CDCl_3$): δ 7.8-7.1, 6.5, 3.9, 3.9, 1.7, 1.6.

b) 1-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

Boc-glycine (0.79 g, 4.5 mmol) was dissolved in a NaOH solution (190 mg, 4.5 mmol) and evaporated and dried in vacuo to afford the sodium salt of Boc-glycine. The sodium salt was dissolved in 10 mL of N,N-dimethylformamide and allowed to react with 1-chloroethyl 2-(6-methoxy-2-naphthyl)propanoate (1.31 g, 4.5 mmol) and potassium iodide (0.80 g, 5.3 mmol). The mixture was stirred at room temperature for 24 h and

the N,N-dimethylformamide was removed in vacuo. The residue was taken up in chloroform and washed with a 5% $NaHCO_3$-solution and then twice with saturated aqueous NaCl-solution, dried over $MgSO_4$ and evaporated. The residue was chromatographed (flash silica gel, 1:2 ethyl acetate: petroleum ether) to give the Boc-protected 1-(glycyloxy)ethyl ester of naproxen (410 mg, 0.93 mmol, 21%) as a viscous oil. The Boc-protected ester (400 mg) was dissolved in dioxane (5 mL) and 4 N HCl/dioxane (4 mL) was added and solution was stirred at room temperature for 4 hours followed by concentration under vacuum. The residue was recrystallized from dioxane to give the 1-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate hydrochloride salt (220 mg, 64 %): mp 149-50 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.71, 7.36, 7.74, 7.20, 7.13, 7.74, 3.90, 3.91, 1.55, 6.95/6.98*, 1.51/1.42, 3.74/3.67; (*two diastereomers, ratio 1:1); HR-MS: Calculated mass for $C_{18}H_{21}NO_5$: 331.142. Measured mass: 331.135.

Example 9

1-(L-phenylalanyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = -CH(CH_3)- ; R_2 = -COCH[$CH_2C_6H_5$]-NH_2)

Synthesized analogously to the example 8 from naproxen acid chloride (5.1 mmol) and acetaldehyde to yield 1-chloroethyl 2-(6-methoxy-2-naphthyl)propanoate, which was reacted with the sodium salt of Boc-L-phenylalanine (prepared analogously from Boc-L-phenylalanine as described) to afford the Boc-protected 1-(L-phenylalanyloxy)ethyl ester of naproxen as oil (740 mg, 27%). The Boc-protected ester (600 mg) was dissolved in dioxane (5 mL) and 4 N HCl/dioxane (4 mL) was added and solution was stirred at room temperature for 4 hours followed by concentration under vacuum. The residue was recrystallized from tetrahydrofuran to give the hydrochloride salt of 1-(L-phenylalanyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate (120 mg, 24%) mp 176 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.68/7.66*, 7.38/7.36, 7.69/7.74, 7.14/7.13, 7.09/7.08, 7.69/7.72, 3.87/3.86, 3.90/3.89, 1.57/1.54, 6.95/6.91, 1.43/1.40, 4.22/4.15, 3.06/2.86, 7.20-7.14, 7.32-7.28, 7.28-7.24 (*two diastereomers ratio 7:3); HR-MS: Calculated mass for $C_{25}H_{27}NO_5$: 421.189. Measured mass: 421.181.

Example 10

2-[2-(1-morpholinyl)acetyloxy]ethyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH_2CH_2-$; R_3 = $-CH_2-$; R_4 - R_5 = $-CH_2CH_2OCH_2CH_2-$

2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate (0.32 g, 1.2 mmol) and 2-(1-morpholinyl)acetic acid (0.17 g, 1.2 mmol), 4-(N,N-dimethylamino)pyridine (0.15 mg, 1.2 mmol) and N,N'-dicyclohexylcarbodiimide (0.41 g, 2.0 mmol) in dry dichloromethane (30 mL) was stirred at room temperature for 36 h. The precipitated dicyclohexylurea was filtered off and the filter cake was washed with dichloromethane. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography eluting with 3% methanol in dichloromethane to give the desired compound (0.20 g, 40%) as a solid: mp 78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68, 7.39, 7.13, 4.27, 3.91, 3.87, 3.69, 3.00, 2.43, 1.58. HRMS: *m/z* 401.1918, calcd for $C_{22}H_{27}NO_6$ 401.1838.

Example 11

4-[2-(1-morpholinyl)acetyloxy]butyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH_2CH_2CH_2CH_2-$; R_3 = $-CH_2-$; R_4 - R_5 = $-CH_2CH_2OCH_2CH_2-$

The compound was prepared as described in the example 10 from 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (0.96 g, 3.2 mmol) and 2-(1-morpholinyl)acetic acid (0.46 g, 3.2 mmol) to give the desired compound (0.28 g, 20%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68, 7.39, 7.13, 4.07, 3.92, 3.84, 3.74, 3.14, 2.55, 1.62, 1.58. HRMS: *m/z* 429.2281, calcd for $C_{24}H_{31}NO_6$ 429.2151.

Example 12

2-[2-(4-methyl-1-piperazinyl)acetyloxy]ethyl2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH_2CH_2-$; R_3 = $-CH_2-$; R_4 - R_5 = $-CH_2CH_2N(CH_3)CH_2CH_2-$

2-hydroxyethyl 2-(6-methoxy-2-naphthyl)propanoate (0.39 g, 1.4 mmol) and 2-(4-methyl-1-piperazinyl)acetic acid (0.22 g, 1.4 mmol), 4-(N,N-dimethylamino)pyridine (0.15 mg, 1.2 mmol) and N,N'-dicyclohexylcarbodiimide (0.44 g, 2.1 mmol) in dry dichloromethane (30 mL) was stirred at room temperature for 36 h. The precipitated dicyclohexylurea was filtered off and the filter cake was washed with dichloromethane. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography eluting with 20% methanol in dichloromethane to give the desired compound (0.41 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67, 7.38, 7.13, 4.23, 3.91,

3.86, 3.08, 2.54, 2.33, 1.57. HRMS: *m/z* 414.2208, calcd for $C_{24}H_{31}NO_6$ 414.2155.

Example 13

4-[2-(4-methyl-1-piperazinyl)acetyloxy]butyl 2-(6-methoxy-2-naphthyl)propanoate

(R_1 = $-CH_2CH_2CH_2CH_2-$; R_3 = $-CH_2-$; R_4 - R_5 = $-CH_2CH_2N(CH_3)CH_2CH_2-$

The compound was prepared as described in the example 12 from 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (0.17 g, 0.6 mmol) and 2-(4-methyl-1-piperazinyl)acetic acid (0.10 g, 0.6 mmol) to give the desired compound (0.09 g, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68, 7.39, 7.13, 4.07, 3.91, 3.84, 3.16, 2.62, 2.56, 2.33, 1.62, 1.57. HRMS: *m/z* 442.2569, calcd for $C_{25}H_{34}N_2O_5$ 442.2468.

Example 14

4-[3-(4-methyl-1-piperazinyl)propionyloxy]butyl-2-(6-methoxy-2-naphthyl)propanoate (R_1 = $-CH_2CH_2CH_2CH_2-$; R_3 = $-CH_2CH_2-$; R_4 - R_5 = $-CH_2CH_2N(CH_3)CH_2CH_2-$)

The compound was prepared as described in the example 12 from 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (2.0 g, 6.6 mmol) and 3-(4-methyl-1-piperazinyl)propionic acid (1.2 g, 6.9 mmol) to give the desired compound (2.45 g, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.11 (6H, aromatic), 4.10, 4.02, 3.91, 3.85, 2.66, 2.45, 2.6-2.3 (8H, $N(CH_2CH_2)_2N$), 2.27, 1.7-1.5 (4H, CCH_2CH_2C), 1.57, HRMS: *m/z* 456.2728, calcd for $C_{26}H_{36}N_2O_5$ 456.2624.

Example 15

4-[4-(4-methyl-1-piperazinyl)butyryloxy]butyl 2-(6-methoxy-2-naphthyl)propanoate (R_1 = $-CH_2CH_2CH_2CH_2-$; R_3 = $-CH_2CH_2CH_2-$; R_4 - R_5 = $-CH_2CH_2N(CH_3)CH_2CH_2-$)

The compound was prepared as described in the example 12 from 4-hydroxybutyl 2-(6-methoxy-2-naphthyl)propanoate (1.0 g, 3.3 mmol) and 4-(4-methyl-1-piperazinyl)butyric acid (0.61 g, 3.3 mmol) to give the desired compound (1.17 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.11 (6H, aromatic), 4.10, 4.00, 3.91, 3.85, 2.6-2.3 (8H, $N(CH_2CH_2)_2N$), 2.33, 2.29, 2.27, 1.78, 1.7-1.5 (4H, CCH_2CH_2C), 1.57, HRMS: *m/z* 470.2593, calcd for $C_{27}H_{38}N_2O_5$ 470.2781.

TEST METHODS

The compounds of the present invention have been tested in the following tests. A prodrug with good permeation across biological membranes (especially across the skin) should exhibit optimum lipophilicity (partition coefficient) in combination with adequate aqueous solubility. The skin consists of multilamellar bilayers and thus the prodrug must have adequate water-solubility to be able to cross the lipid-aqueous interfaces. In addition to optimum lipophilicity and aqueous solubility, the prodrugs should be stable enough against chemical degradation and release enzymatically the active parent drug during or after absorption/penetration.

1) Aqueous solubility

Method

The aqueous solubilities of the present compounds were determined in phosphate buffer (0.16 M) at pH 5.0 and 7.4 at room temperature. Excess amounts of each compound were added to 1-4 ml of solvents. The mixtures of phosphate buffers were vortexed either for 60 min (pH 5.0) or for 20-30 min (pH 7.4), filtered (Millipore 0.45 μm) and diluted with an appropriate amount of phosphate buffer before HPLC analysis. The pH of the mixtures was checked in the middle of the vortexing and adjusted, if necessary.

Results

Aqueous solubilities of the present compounds are shown in Table 1. Due to the acid character of naproxen (pKa 4.15), it is more water soluble at pH 7.4 than at pH 5.0. In contrast to naproxen, the prodrugs are more soluble in acidic than in neutral aqueous solutions due to the ionizable basic group in the promoiety. Therefore, the present prodrugs possess adequate aqueous solubilities compared to naproxen at pH 7.4. At pH 5.0, most prodrugs showed an increase in aqueous solubility compared to naproxen.

2) Lipophilicity

Method

The lipophilicities of the present compounds were evaluated by apparent partition coefficients (log P_{app}), and were determined at room temperature in a 1-octanol-phosphate buffer system at pH 5.0 and 7.4. The phosphate buffer and 1-octanol phases were saturated before use by stirring vigorously for 24 h at room temperature. A known concentration of prodrug in phosphate buffer (0.16 M) was shaken with a suitable volume of 1-octanol to achieve equilibrium. After shaking (0.5 – 1 hours), the phases were separated by centrifugation at 14000 rpm for 5 min before HPLC analysis.

Results

The log P_{app}-values of the present compounds are shown in Table 1. All the prodrugs are clearly more lipophilic than naproxen at pH 7.4. In addition, the prodrugs maintained lipophilicities comparable to that of naproxen at pH 5.0.

Table 1. Aqueous solubilities (mean ± SD; n = 2-4) and apparent partition coefficients (log $P_{app,}$ mean ± SD; n = 2-3) of naproxen and its various prodrugs.

Compound	Aqueous Solubility at pH 7.4 (mM)	Aqueous Solubility at pH 5.0 (mM)	log P_{app} at pH 7.4	log P_{app} at pH 5.0
Naproxen	101.9 ± 1.3	0.40 ± 0.04	0.30 ± 0.03	2.38 ± 0.02
example 1	4.73 ± 1.06	10.38 ± 0.75	2.80 ± 0.04	0.67 ± 0.01
example 2	0.15 ± 0.01	0.31 ± 0.04	3.30 ± 0.07	2.16 ± 0.02
example 3	0.15 ± 0.01	1.69 ± 0.32	3.37 ± 0.01	2.13 ± 0.02
example 4	0.03 ± 0.00	0.18 ± 0.01	2.93 ± 0.01	2.30 ± 0.00
example 5	3.24 ± 0.05	5.87 ± 1.04	2.25 ± 0.05	0.99 ± 0.04
example 6	0.03 ± 0.00	1.07 ± 0.02	2.56 ± 0.07	2.72 ± 0.04
example 7	0.004±0.001	0.10 ± 0.04	2.90 ± 0.10	2.91 ± 0.06
example 8	nd	3.66 ± 0.01	nd	1.37 ± 0.00
example 9	nd	0.32 ± 0.02	nd	3.04 ± 0.00
example 10	0.07 ± 0.002	0.05 ± 0.00	2.14 ± 0.08	2.62 ± 0.00
example 12	4.11 ± 0.37	5.33 ± 0.90	1.30 ± 0.25	0.43 ± 0.05
example 13	8.79 ± 0.90	16.20 ± 1.22	1.30 ± 0.05	0.94 ± 0.05
example 14	432.4 ± 27.5	141.6 ± 27.0	3.04 ± 0.07	1.20 ± 0.06
example 15	50.0 ± 1.9	61.0 ± 8.8	2.69 ± 0.06	1.41 ± 0.02

nd = values were not determined due to poor aqueous stability of prodrugs

3) Chemical stability

Method

The chemical stability studies were performed in an aqueous phosphate buffer solution of pH 7.4 and pH 5.0 (0.16M, ionic strength 0.5) at 37 °C. The solutions of prodrugs were prepared by adding an appropriate amount of the compound to the preheated buffer. After vortexing, the solutions were maintained at a constant temperature of 37 °C. At appropriate intervals, samples were taken and analyzed for remaining prodrug by HPLC.

Results

Half-lives ($t_{1/2}$) for the degradation of prodrugs in aqueous solutions are shown in Table 2. The degradation of all prodrugs followed pseudo-first-order kinetics at pH 5.0 and 7.4. The chemical stability of the prodrugs was substantially greater at pH 5.0 than at 7.4. Besides, the addition of ethanol increased the chemical stability of the prodrugs (data not shown).

4) Enzymatic hydrolysis

Method

The susceptibility of prodrugs to undergo enzymatic hydrolysis was studied in human serum by diluting to 80% with 0.16 M phosphate buffer of pH 7.4 at 37 °C. The reactions were initiated by adding the prodrug to phosphate buffer and then preheated serum was added. The solutions were kept at a constant temperature of 37 °C and at appropriate intervals, 0.5 ml samples of serum/buffer mixture were withdrawn and added to 1.0 ml of ethanol in order to precipitate protein from the serum homogenate. After immediate mixing and centrifugation, the resulting clear supernatant was analyzed with HPLC for remaining prodrug and formed parent compound.

Results

Half-lives ($t_{1/2}$) for the degradation of prodrugs in 80% human serum are shown in Table 2. The hydrolysis of all prodrugs followed pseudo-first-order kinetics at pH 7.4.

The prodrugs were highly susceptible to serum catalyzed hydrolysis and they rapidly released parent active compound. The hydrolysis of the acyloxyalkyl esters takes place enzymatically by attack on the carbonyl of the parent drug and on the carbonyl of the promoiety. The bioconversion of the prodrugs is schematically presented below.

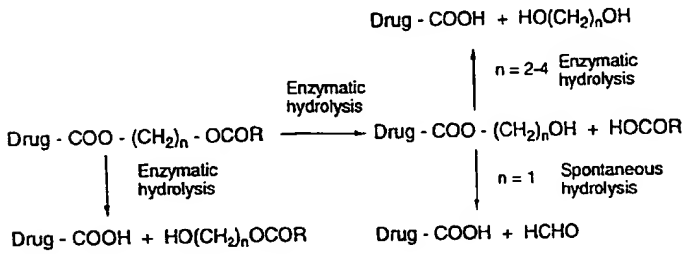


Table 2. Rate of hydrolysis of prodrugs in buffer solutions (pH 7.4 and 5.0) and in 80% human serum (pH 7.4) at 37 °C.

Compound	$t_{1/2}$ (h) phosphate buffer pH 7.4	$t_{1/2}$ (h) phosphate buffer pH 5.0	$t_{1/2}$ (min) 80 % human serum
example 1	2.6	233	19
example 2	3.2	84	10
example 3	13	648	8
example 4	3.7	53	9
example 5	4.2	115	13
example 6	81	3552	5
example 7	23	72	13
example 8	0.5	5	4
example 9	0.9	7	9
example 10	34	161	20
example 11	-	-	12
example 12	58	1596	25
example 13	182	1870	3
example 14	17	432	3
example 15	48	893	1

5) In vitro skin penetration

Method

The in vitro drug permeation studies were performed in Franz-type vertical diffusion cells (Amie systems., USA) with an effective diffusional area of 0.71 cm^2. The thawed and rehydrated skin specimens were mounted between chambers with the stratum corneum facing the donor chamber. The receptor chamber was filled with isotonic phosphate buffer (0.05 M, pH 7.4) containing 0.02% sodium azide as a preservative. Samples of naproxen and its prodrugs were applied as suspensions or solutions in this buffer solution or in isotonic phosphate buffer of pH 5.0 (0.05 M). The receptor phase was stirred magnetically and kept at a constant temperature of 37 °C throughout the study. The receptor compartment was sampled at appropriate time intervals with replacement with fresh buffer solution. The samples were assayed for drug concentrations by HPLC and corrected for dilution attributable to the sampling procedure. The skin flux-values (J_{ss}) for rate of delivery of naproxen and its prodrugs were determined by plotting the cumulative amounts (in nmol) of the parent drug, intermediates and intact prodrugs measured in the receptor phase against the time and dividing the slopes of the steady-state position by the surface area of the diffusion cell.

Results

The steady-state fluxes (J_{ss}) for prodrugs are shown in Table 3. The diffusion experiments showed that skin permeation of naproxen can be improved by prodrugs. Prodrugs improved skin permeation of naproxen with a maximum enhancement of 4-fold at pH 7.4 and 3-fold at pH 5.0.

Table 3. The steady-state fluxes (mean ± SE, n=3–10) for delivery of total naproxen species through excised human skin in vitro from isotonic phosphate buffer (0.05 M, pH 5.0 or pH 7.4) at 37 °C.

Compound	Flux (nmol/cm2/h) pH 7.4	Flux (nmol/cm2/h) pH 5.0
Naproxen	6.5 ± 0.6	1.6 ± 0.2
example 1		4.0 ± 0.4
example 2		1.6 ± 0.0
example 3		5.1 ± 0.4
example 5		1.5 ± 0.1
example 6		1.8 ± 0.3
example 10	0.67 ± 0.02	0.63 ± 0.04
example 12	24.6 ± 1.0	2.2 ± 0.1
example 13	7.2 ± 0.1	0.2 ± 0.0
example 14	7.7 ± 1.3	0.6 ± 0.0
example 15	13.2 ± 1.6	1.2 ± 0.2

6) Conclusions

The results show that the novel compounds of the present invention

1) are lipophilic at pH 5 and 7. In case of dermal application, the adequate lipophilicity of the prodrug at the pH range 5–7 is necessary due to the structure of the skin; the pH of outer surface of skin is about 5 but will increase up to 7 in its inner parts.

2) have adequate aqueous solubility.

3) are adequately stable against chemical hydrolysis in aqueous solutions and thus they

enable the preparation of water-based formulations.

4) are hydrolyzed enzymatically to the parent active drug, the NSAIDs.

5) improve significantly the permeation of parent drug across the skin. The improved skin penetration is due to the lipophilic character of the prodrugs at pH 5-7 in combination with adequate aqueous solubility. A lipohilic prodrug with poor aqueous solubility is not able to cross the lipid-aqueous phase interfaces of multilamellar bilayers.

The results also show that aqueous solubility, lipophilicity, enzymatic hydrolysis (and thus the formation of the parent drug) and membrane penetration of the present compounds can be easily regulated by changing the chemical group attached to the parent drug.

The improved skin permeation allows for improved topical administration of NSAIDs. Topical administration is desirable because the prodrug will release the parent active drug at the site of inflammation and high systemic drug concentration can be avoided.

CLAIMS

1. Aminoacyloxyalkyl prodrugs of non-steroidal anti-inflammatory carboxylic acids of formula

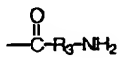
(I)

wherein:

R-COO- represents the acyloxy residue of a carboxylic acid group containing non-steroidal anti-inflammatory agent, i.e. of a non-steroidal anti-inflammatory carboxylic acid R-COOH,

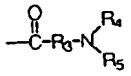
R_1 represents a saturated or unsaturated, a straight-chain, branched or cyclic alkylene or alkylidene group of 1 to 8 carbon atoms, which can optionally be substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono- or dialkylamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy,

R_2 is an aminoacyl residue of a synthetic or natural amino acid of the formula



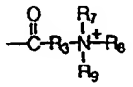
wherein R_3 represents a straight-chain or branched alkylene or alkylidene group of 1 to 8 carbons, which may be substituted with 1 to 3 groups selected from amino, mono- or dialkylamino, acylamino, hydroxyl, thiol, methylthiol, carboxyl, and phenyl,

or R_2 is a secondary or tertiary aminoacyl group of the formula



wherein R_3 is as hereinabove defined; R_4 and R_5 are the same or different and are selected from hydrogen, a straight-chain or branched C_1-C_6-alkyl group, which is optionally substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono- or dialkyamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl,

cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy, or R_4 and R_5, together with the nitrogen, form a cyclic heteroalkyl radical or a heteroaryl radical, or R_2 is a quaternary aminoacyl group of the formula

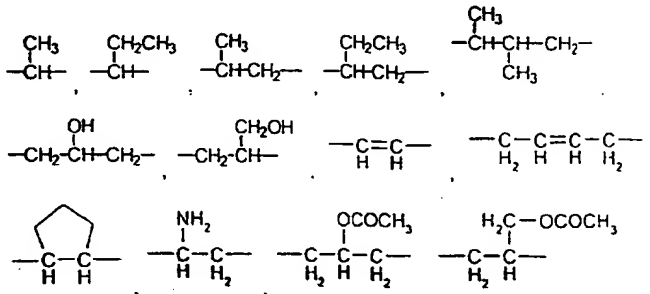


wherein R_3 is as hereinabove defined and R_7, R_8 and R_9 are the same or different and are selected from hydrogen, a straight–chain or branched C_1–C_6–alkyl group, which optionally is substituted with 1 to 3 groups selected from halogen, hydroxyl, thiol, amino, mono– or dialkyamino, acylamino, carboxyl, alkylcarboxyl, acyl, aryl, aroyl, aralkyl, cyano, nitro, alkoxy, alkenyloxy, alkylcarbonyloxy and arylcarbonyloxy, as well as the nontoxic pharmaceutically acceptable acid addition salts thereof.

2. The prodrugs according to claim 1, characterized in that R–COO– is the acyloxy residue of naproxen; ketoprofen; ibuprofen; fenoprofen; flurbiprofen; oxaprofen; diclofenac; tolmetin; tolfenamic acid; mefenamic acid; sulindac; indomethacin; salicylic acid; acetylsalicylic acid; diflunisal; loxoprofen; indoprofen; pirprofen; clidanac; fenclorac; meclofenamate; benoxaprofen; carprofen; isofezolac; aceclofenac; fenbufen; etodolic acid; fleclozic acid; amfenac; efenamic acid; bromfenac; fenclofenac; alcofenac; orpanoxin; zomopirac; flufenamic acid; niflumic acid; pranoprofen; zaltoprofen; suprofen; and ketorolac.

3. The prodrugs according to claim 1, **characterized** in that R_1 is a saturated or unsaturated, straight-chain or branched alkylene or alkylidene group with 1 to 8 carbon atoms.

4. The prodrugs according to claim 1 or 2, **characterized** in that R_1 is methylene, ethylene, trimethylene, tetramethylene



5. The prodrugs according to claim 1, **characterized** in that R_2 is an aminoacyl residue of a synthetic or natural amino acid, or a secondary or tertiary aminoacyl group, as defined in claim 1.

6. The prodrugs according to any one of the claims 1 to 5, **characterized** in that R_2 is the aminoacyl residue of alanine, glycine, glycylglycine, arginine, cysteine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, hydroxyproline, serine, valine, tryptophan, tyrosine, threonine, ornithine, α-aminobutyric acid, norvaline, norleucine.

7. The prodrugs according to claim 1, **characterized** in that R_4 and R_5 are selected from hydrogen or a straight-chain or branched C_1-C_6-alkyl group, or they form together a cyclic heteroalkyl radical.

8. The prodrugs according to any one of the claims 1 to 7, **characterized** in that R_4 and R_5 together form a cycloheteroalkyl radical selected from the group consisting of morpholinyl, thiomorpholinyl, 1-pyrrolidinyl, piperidinyl, piperazinyl or 4-alkyl-1-piperazinyl, such as 4-methyl-1-piperazinyl.

9. The prodrugs according to any one of the claims 1 to 6, **characterized** in that R_4 and R_5 together form a heteroaryl radical selected from the group consisting of imidazolyl, indoxyl, indolizinyl, oxazolyl, thiazolyl or 1-pyrazolyl.

10. The prodrugs according to claim 3, **characterized** in that R_1 is unsubstituted alkylene or alkylidene with 1 to 6 C-atoms, preferably 1-4 C-atoms.

11. The prodrugs according to claim 1, **characterized** in that R_3 is unsubstituted alkylene or alkylidene with 1 to 6 C-atoms, or alkylidene with 1-6 C-atoms substituted by phenyl.

12. The prodrugs according to claim 10 or 11, **characterized** in that R_2 is the aminoacyl residue of glycine, leucine, isoleucine or phenylalanine.

13. The prodrugs according to claim 10 or 11, **characterized** in that R_4 and R_5 together form a morpholinyl or optionally alkyl-substituted piperazinyl, such as a 4-methyl-1-piperazinyl ring.

14. The prodrugs according to any one of the preceding claims, **characterized** in that R-COO- is the acyloxy residue of naproxen, ketoprofen, ibuprofen, fenoprofen, flurbiprofen, oxaprofen, diclofenac, indomethacin, loxoprofen, indoprofen, pirprofen, clidanac, fenclorac, meclofenamate, benoxaprofen, carprofen, aceclofenac, fenbufen, fleclozic acid, pranoprofen, zaltoprofen, suprofen or ketorolac.

15. The prodrugs according to any one of the preceding claims, **characterized** in that RCOO- means the acyloxy residue of naproxen.

16. The prodrugs according to any one of the preceding claims selected from the group consisting of

2-(glycyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

2-(L-isoleucyloxy)ethyl 2-(6-methoxy-2-naphthyl)propanoate

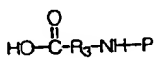
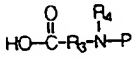
2-[2-(4-methyl-1-piperazinyl)acetyloxy]ethyl 2-(6-methoxy-2-naphthyl)propanoate

4-[2-(4-methyl-1-piperazinyl)acetyloxy]butyl 2-(6-methoxy-2-naphthyl)propanoate

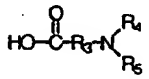
17. Process for preparing the prodrugs according to any one of the preceding claims, **characterized** in that

a) the carboxyl function of a non-steroidal anti-inflammatory carboxylic acid R-COOH or its acid salt of the formula $R\text{-}COO^{-}\text{-}M^{+}$, wherein R has the meaning given in claim 1, is esterified with a compound of the formula $X\text{-}R_1\text{-}OH$, wherein X is a suitable leaving group, e.g., chlorine, tosylate, iodine etc., preferably bromine and R_1 is as defined in claim 1, to yield the intermediate with the formula $R\text{-}COO\text{-}R_1\text{-}OH$(II), or

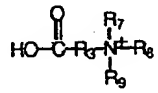
a_1) an acid of the formula R-COOH or a reactive derivative thereof of the formula R-COZ, wherein Z is a halide or an anhydride or mixed anhydride residue, is reacted with a compound of the formula $HO\text{-}R_1\text{-}OH$, wherein R_1 is as defined in claim 1, when the acid is used, in the presence of a condensing agent, to yield the intermediate with the formula $R\text{-}COO\text{-}R_1\text{-}OH$ (formula II),
which intermediate II is thereafter reacted in the presence of a condensing agent with the protected primary or secondary amino acid of the formula,

 or 

wherein R_3 and R_4 are as defined in claim 1 and P is a protecting group,
or with a tertiary amino acid of the formula,



wherein R_3, R_4 and R_5 are as defined in claim 1,
or with a quaternary amino acid of the formula:



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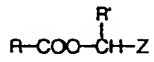
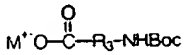
wherein R_3, R_7, R_8 and R_9 are as defined in claim 1, to give the desired prodrug compound, which compound is optionally converted to its acid addition salt, or

b) a halide ester of a nonsteroidal antiinflammatory carboxylic acid of the formula



wherein R' has the meaning of hydrogen, a straight or branched alkyl group, preferably an optionally substituted lower alkyl group with 1 - 6 C-atoms as defined for R_4 and R_5, or an optionally substituted aryl or aralkyl group, and Z is a halide, preferably a chloride, is reacted with an acid salt, preferably an alkaline metal or amine salt of a Boc-protected amino acid of the formula



and the Boc-protective group is removed with an anhydrous acid, to give a compound of the formula I, and the compound obtained, if desired, is converted to its acid addition salt.

18. Pharmaceutical composition, **characterized** in that it contains a therapeutically effective amount of a prodrug according to any one of the claims 1 to 16, and at least one pharmaceutically acceptable carrier, vehicle, and/or adjuvant.

19. The pharmaceutical composition according to claim 18, **characterized** in that it contains a carrier, vehicle and/or adjuvant suitable for topical use.

20. A prodrug according to any one of the claims 1 to 16, for use as a therapeutically effective agent.

21. The prodrug according to claim 20 for topical use.

22. A method for the preparation of a medicament with anti-inflammatory activity, **characterized** in that it contains a prodrug according to any one of the claims 1 to 16 as the active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00855

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 229/02, C07C 229/08, C07C 229/36, C07D 295/145, A61K 31/216, A61K 31/395, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Pharmaceutical Research, Volume 16, No 8, 1999, J. RAUTIO ET AL, "Synthesis and in Vitro Evaluation of Aminoacyloxyalkyl Esters of 2-(6-methoxy-2-naphthyl)propionic Acid as Novel Naproxen prodrugs for Dermal Drug Delivery" page 1172 - page 1178 --	1-22
A	EP 0124925 A1 (FARMA RESA SRL), 14 November 1984 (14.11.84) --	1-22
A	US 5607966 A (M.R. HELLBERG ET AL), 4 March 1997 (04.03.97) --	1-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2000	01 -02- 2000
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell / MR Telephone No. +46 8 782 25 00

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 99/00855

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5498729 A (A.J. DOMB), 12 March 1996 (12.03.96) --	1-22
A	Inflammopharmacology, Volume 1, No 3, 1992, (Netherlands), M.-F. OTIS ET AL, "Synthesis and pharmacological evaluation of amide derivatives of non-steroidal anti-inflammatory drugs" page 201 - page 212 --	1-22
A	Indian Drugs, Volume 31, No 2, 1994, J.K. LALLA ET AL, "Naproxen lysinate. III. Safety and efficacy evaluation" page 51 - page 58 --	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI99/00855

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15 in part
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of claims 1-15 is too broadly formulated to permit a complete search. Therefore, the search has mainly been restricted to the exemples. Confer PCT, Article 6.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.
PCT/FI 99/00855

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0124925 A1	14/11/84	AT 23856 T	15/12/86
		ES 531480 A	16/07/85
		IT 1199994 B	05/01/89
		IT 8320523 D	00/00/00
US 5607966 A	04/03/97	AU 689024 B	19/03/98
		AU 4687796 A	19/07/96
		BR 9510460 A	26/05/98
		CA 2207574 A	04/07/96
		CN 1171107 A	21/01/98
		EP 0799219 A	08/10/97
		FI 972621 A	18/06/97
		JP 10511663 T	10/11/98
		NO 972879 A	25/08/97
		US 5643943 A	01/07/97
		US 5811438 A	22/09/98
		US 5925673 A	20/07/99
		WO 9620187 A	04/07/96
US 5498729 A	12/03/96	US 5660851 A	26/08/97
		AU 655762 B	12/01/95
		AU 7182891 A	24/07/91
		CA 2072360 A	27/06/91
		EP 0510080 A	28/10/92
		JP 6501448 T	17/02/94
		WO 9109831 A	11/07/91